IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	PEPYS
Serial No.	:	09/737,544
For	:	TREATMENT AND PREVENTION OF TISSUE DAMAGE
Filed	:	December 18, 2000
Examiner	:	Shengjun Wang
Art Unit	:	1617
Confirmation No.	:	1521

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FILED VIA EFS-WEB
ON AUGUST 31, 2007

SUBMISSION OF POWERPOINT PRESENTATION OF PROF. MARK PEPYS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Dear Sir:

Submitted herewith is the PowerPoint presentation of Prof. Mark Pepys presented during the August 14, 2007 personal interview, for which the Examiner and his SPE are thanked for the courtesies extended.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

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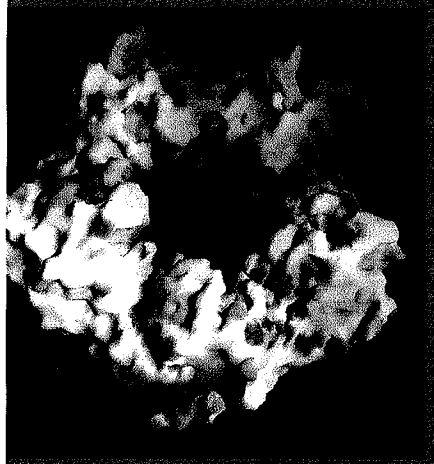
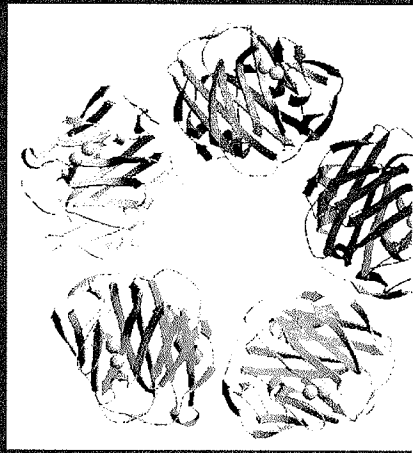


C-reactive protein makes tissue damage worse

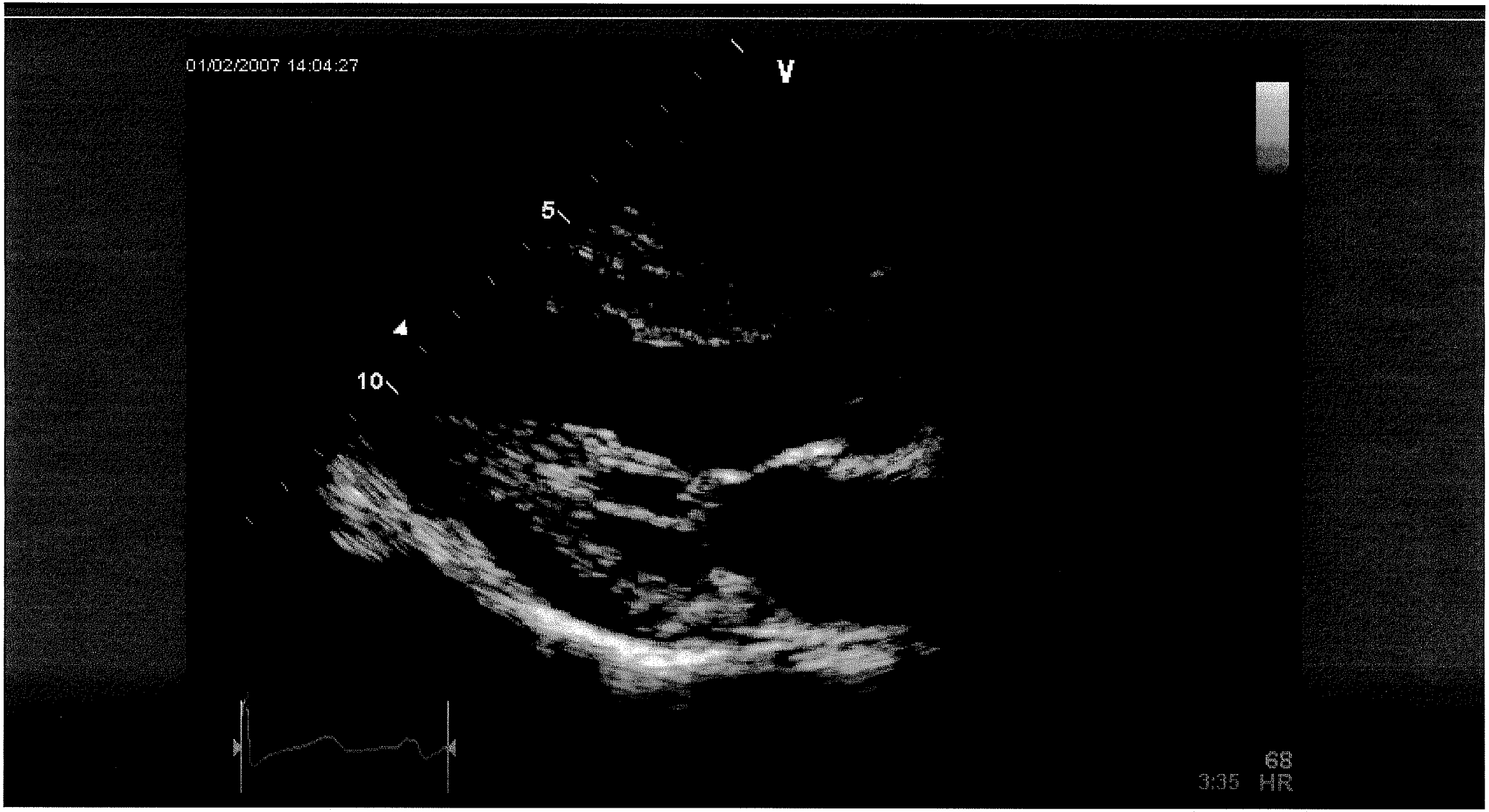


Professor Mark Pepys FRS FMedSci
Chief of Medicine and Director, Centre for Amyloidosis and Acute Phase Proteins
University College London
Director, Pentraxin Therapeutics Ltd

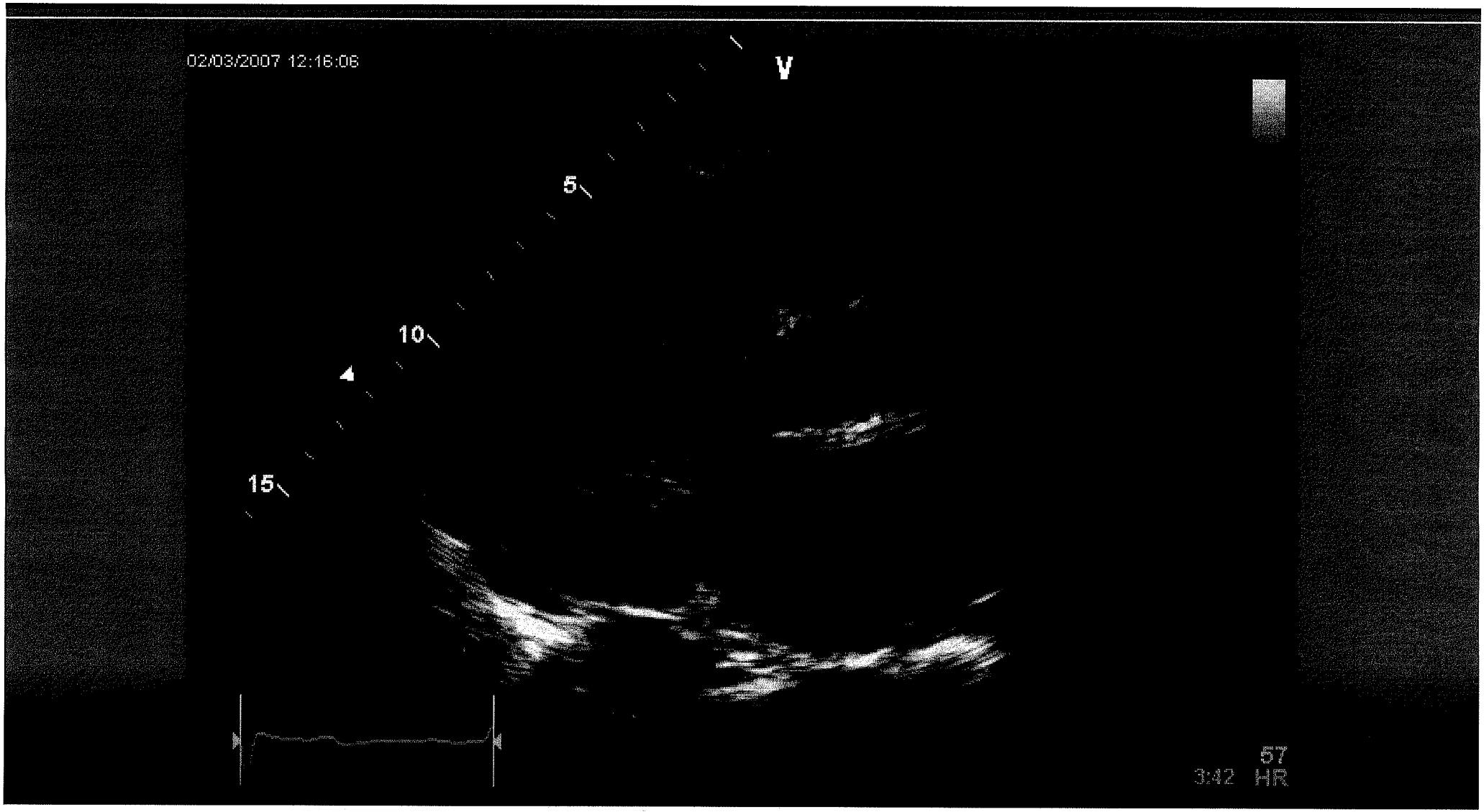
CARDIOVASCULAR DISEASE
The big killer

- 50% or more of all deaths in the USA are due to cardiovascular disease - despite all recent advances: life style, statins, etc
- 1.1 million Americans suffer an acute myocardial infarction each year
- Heart failure after acute myocardial infarction is a massive unmet medical need
- Larger infarcts cause more heart failure

The normal heart



The failing heart

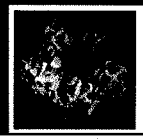


A new approach to cardioprotection – reducing infarct size

Pepys *et al* (2006) Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature,* **440**: 1217-21

Recognition and support for therapeutic CRP targeting

- 1999: New laboratory & clinical building, $18 million
  Pentraxin Therapeutics Ltd: UCL spin-out to hold, develop & commercialize Pepys IP; $2 million invest
- 1999-2004: UK MRC programme grant, $4.6 million
- 2001: Wolfson Foundation, $3.0 million grant
- 2004-9: UK MRC programme grant, $3.6 million
- 2004: NIH NHLBI grant, $864,000
- 2007: RCP Harveian Oration; Royal Society GSK Prize
- 2007: Additional laboratories, $8 million



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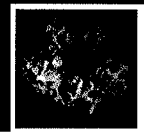
C-reactive protein (CRP)

- The classical acute phase protein
- Non-specific increased production after any injury, infection or inflammation
- Exquisitely sensitive, very wide dynamic range
- No deficiency or polymorphism
- Calcium dependent binding to dead & damaged cells, and to phosphocholine
- Complement activation



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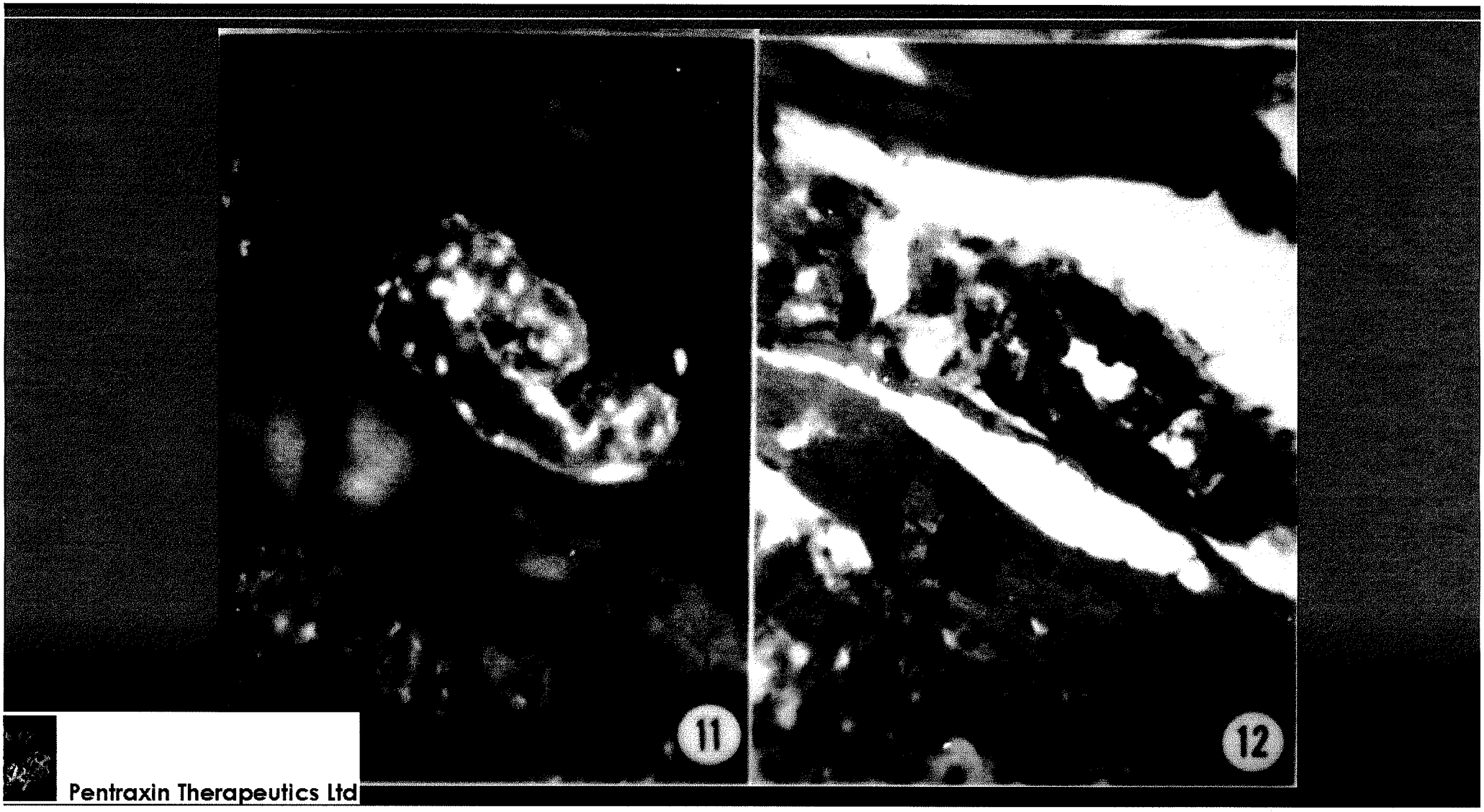
CRP binding to necrotic cardiomyocyte



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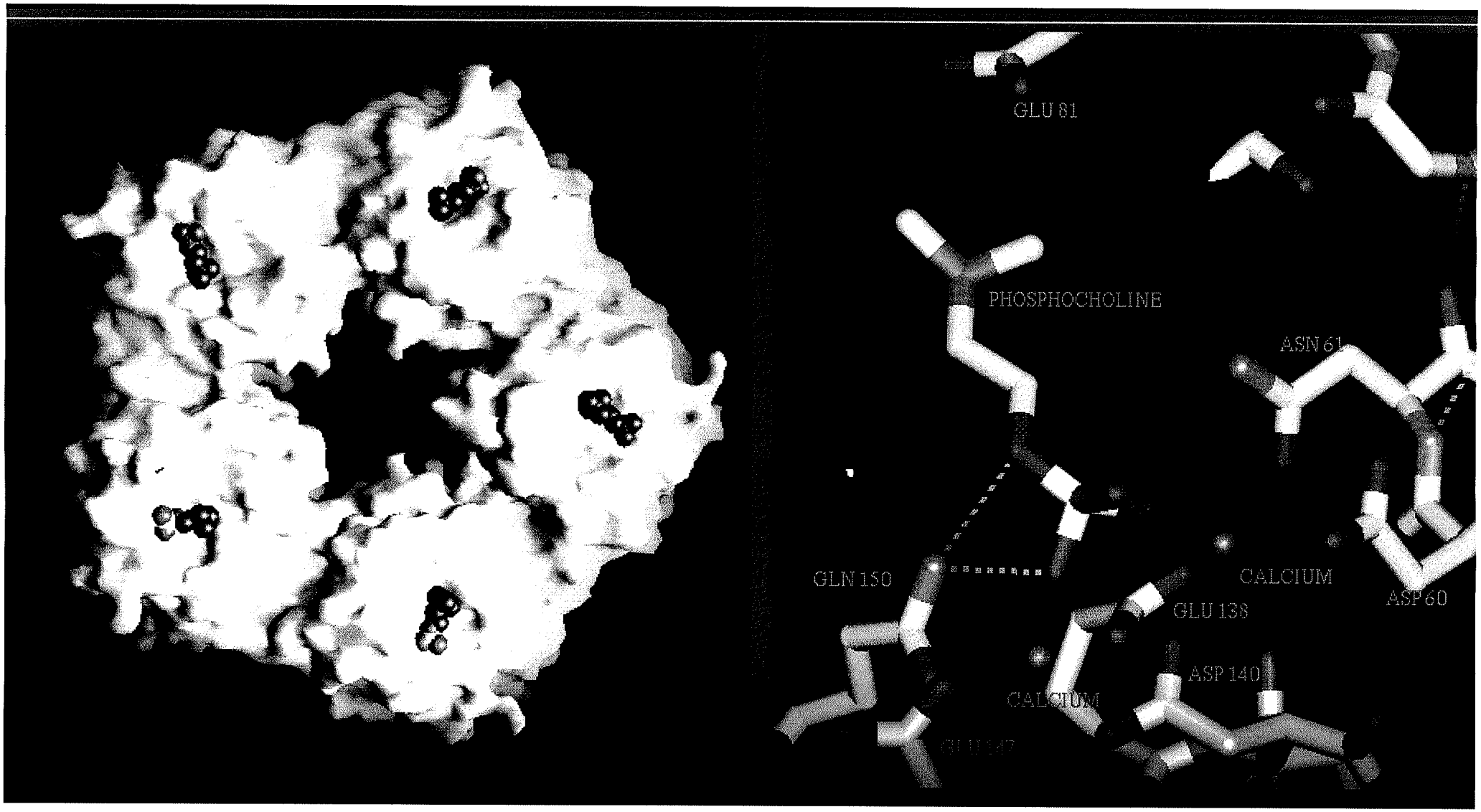
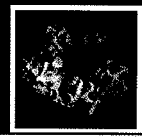
Phosphocholine binding by human CRP



Functions of CRP

- Host defence in innate immunity against infection
- Handling & disposal of damaged cells & lipids
- Anti-inflammatory in some animal models
- No human CRP deficiency or polymorphism, therefore no certain knowledge of function
- Stable conservation across species and no known deficiency suggest beneficial role



CRP & ACUTE MYOCARDIAL INFARCTION

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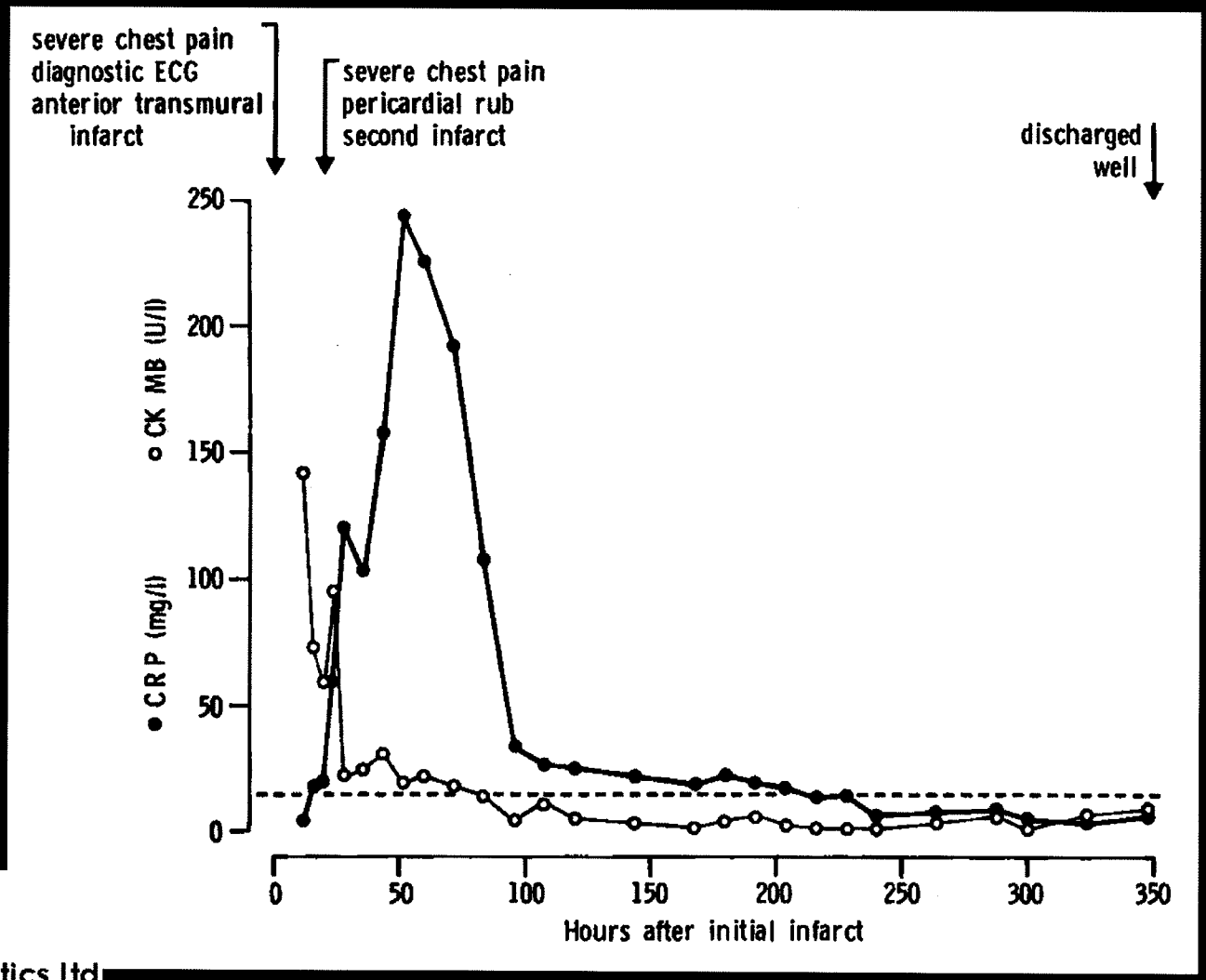
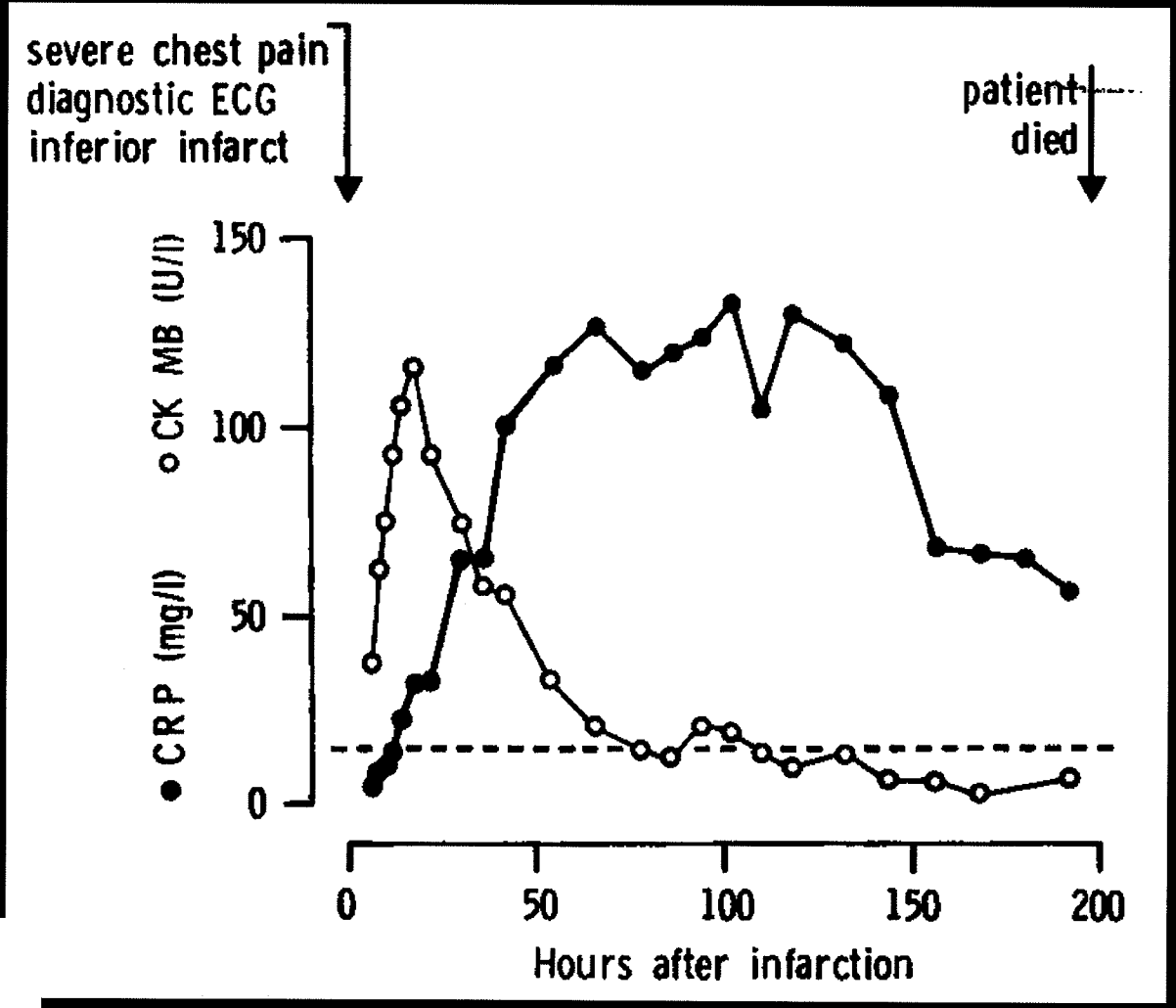
CRP and myocardial infarction

- Circulating CRP concentration rises in response to acute myocardial infarction
- CRP values predict clinical outcome
- BUT this association does NOT prove that CRP causes damage

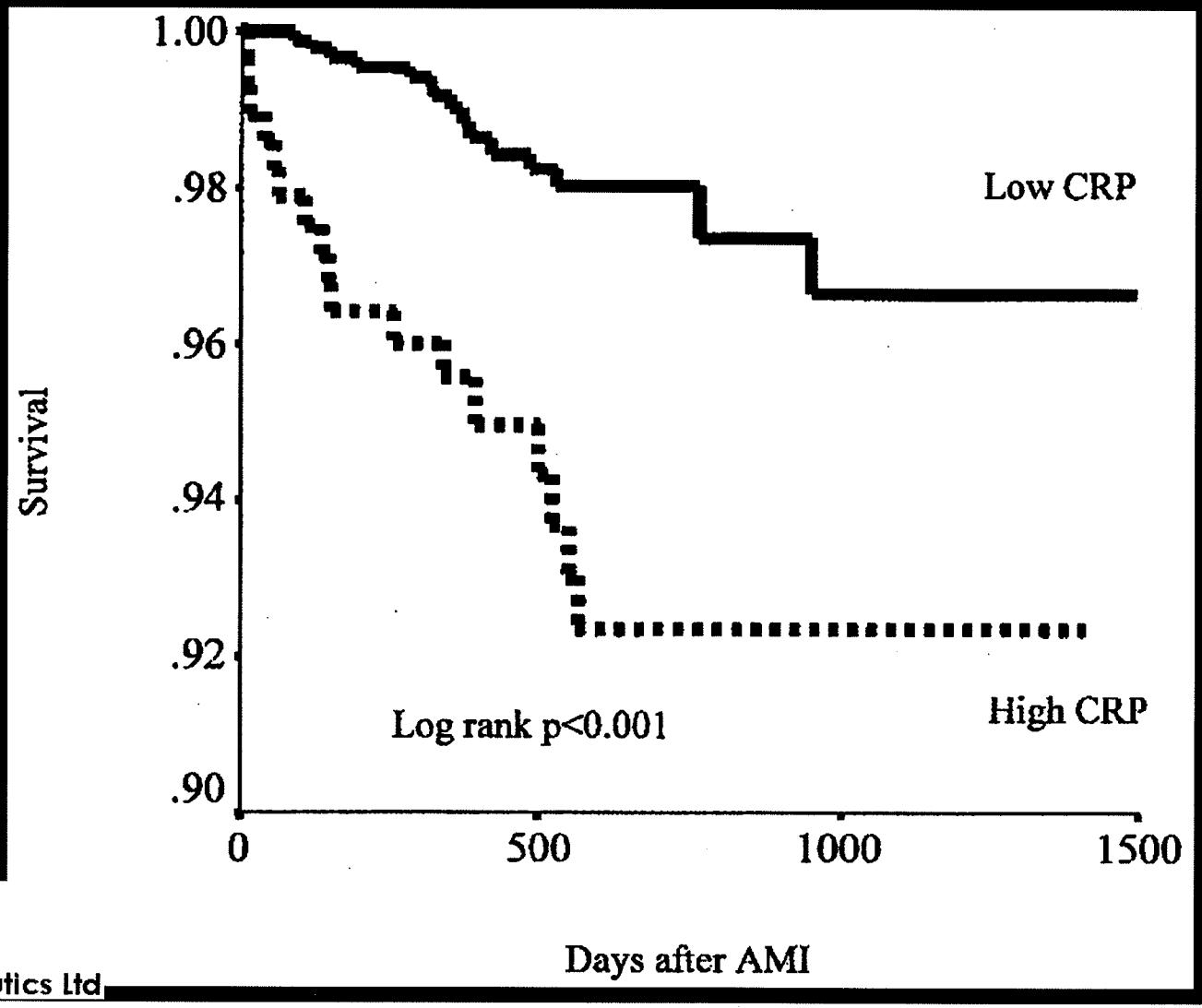
CRP response to acute myocardial infarction – good outcome



CRP response to acute myocardial infarction – poor outcome



CRP 25d post AMI predicts outcome



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CRP 25d post AMI predicts outcome

TABLE 3 Causes of Death

Cause of Death	Low CRP (n = 980)	High CRP (n = 327)	p Value
All-cause death	2.0%	8.9%	<0.001
Cardiovascular death	0.8%	6.4%	<0.001
Pump failure	0.2%	4.0%	<0.001
Sudden death	0.1%	0.3%	0.415
Recurrent infarction	0.0%	1.8%	<0.001
Stroke	0.1%	0.0%	0.563
Cardiac procedure	0.2%	0.0%	0.730
Other	0.2%	0.3%	0.740
Noncardiovascular death	1.1%	2.4%	0.084
Cancer	0.4%	1.2%	0.102
Other	0.7%	1.2%	0.384

CRP & COMPLEMENT IN ACUTE MYOCARDIAL INFARCTION

ASSOCIATION DOES NOT ESTABLISH CAUSALITY

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Complement

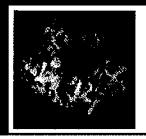
- Complex system of normal plasma proteins
- Cascade of protein cleavage and activation
- Contributes to host defence & resolution of injury
- Can also kill host cells & cause tissue damage

Complement

- Activated by micro-organisms, antibodies, CRP
- Binds to the activator and nearby structures
- Split products attract white cells
- Fixed products kill cells directly
- Fixed products promote phagocytosis, clearance of dead & damaged cells

CRP and complement in myocardial infarction

- CRP & complement are deposited in and around necrotic tissue in myocardial infarcts
- Complement contributes to extent of experimental MI and IR injury but activator unknown
- IS CRP HELPING TO CLEAR THE DAMAGE OR MAKING IT WORSE?



CRP is harmless in healthy individuals

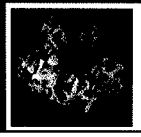
- Injection of huge amounts of pure human CRP has no adverse, inflammatory or tissue damaging effects in healthy animals
- Transgenic expression of human CRP in mice has no adverse, inflammatory or tissue damaging effects in healthy animals

Pepys, M.B. (2005) CRP or not CRP? That is the question. *Arterioscler. Thromb. Vasc. Biol.*, **25:** 1091-1094.

Clapp, B.R., Hirschfield, G.M., Storry, C., Gallimore, J.R., Stidwill, R.P., Singer, M., Deanfield, J.E., MacAllister, R.J., Pepys, M.B., Vallance, P. and Hingorani, A.D. (2005) Inflammation and endothelial function: direct vascular effects of human C-reactive protein on nitric oxide bioavailability. *Circulation*, **111:** 1530-1536.

Pepys, M.B., Hawkins, P.N., Kahan, M.C., Tennent, G.A., Gallimore, J.R., Graham, D., Sabin, C.A., Zychlinsky, A. and de Diego, J. (2005) Proinflammatory effects of bacterial recombinant human C-reactive protein are caused by contamination with bacterial products, not by C-reactive protein itself. *Circ. Res.*, **97:** e97-103.

Lowe, G.D.O. and Pepys, M.B. (2006) C-reactive protein and cardiovascular disease: weighing the evidence. *Curr. Atheroscler. Rep.*, **8:** 421-428.



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THE FIRST DEMONSTRATION OF DAMAGE CAUSED BY CRP

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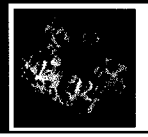
Is human CRP pathogenic *in vivo?*

- Human CRP binds to ligands exposed in damaged tissue and activates human and rat complement
  page 1 paragraph 2
- Rat CRP binds to similar ligands but does not activate rat complement
- Injection of human CRP into rats: excellent model of possible effects of human CRP *in vivo* in humans
  page 8 paragraphs 74, 80
- Occlude coronary or cerebral artery in rats, inject human CRP, monitor severity of tissue damage
  page 8 paragraph 74



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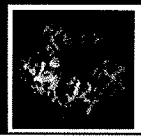
Human CRP increases MI size in rats

Treatment	Infarct size % LV median (range)
Vehicle n=8	11.25 (10.8-15.8)
CRP n=9	19.9 (13.8-32.5)

P value: MW U-test, 0.01; t-test, 0.002

Specific for human CRP
Complement dependent
Human CRP and rat complement deposited in the infarct



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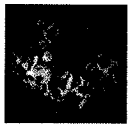
Human CRP increases MI size in rats

control

CRP



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Human CRP increases MI size in rats

Treatment	Day 5 survivors	Infarct size % mean (SD)	Bonferroni t-test
Buffer	5/ 5	14.5 (1.1)	
Human CRP	4/ 5	21.2 (2.0)	P=0.0007
Buffer	3/ 3	12.8 (0.9)	
Human SAP	5/ 5	12.4 (1.9)	
Human CRP	3/ 5	17.6 (0.4)	P=0.0022

Infarcts 38-46% larger in rats given human CRP

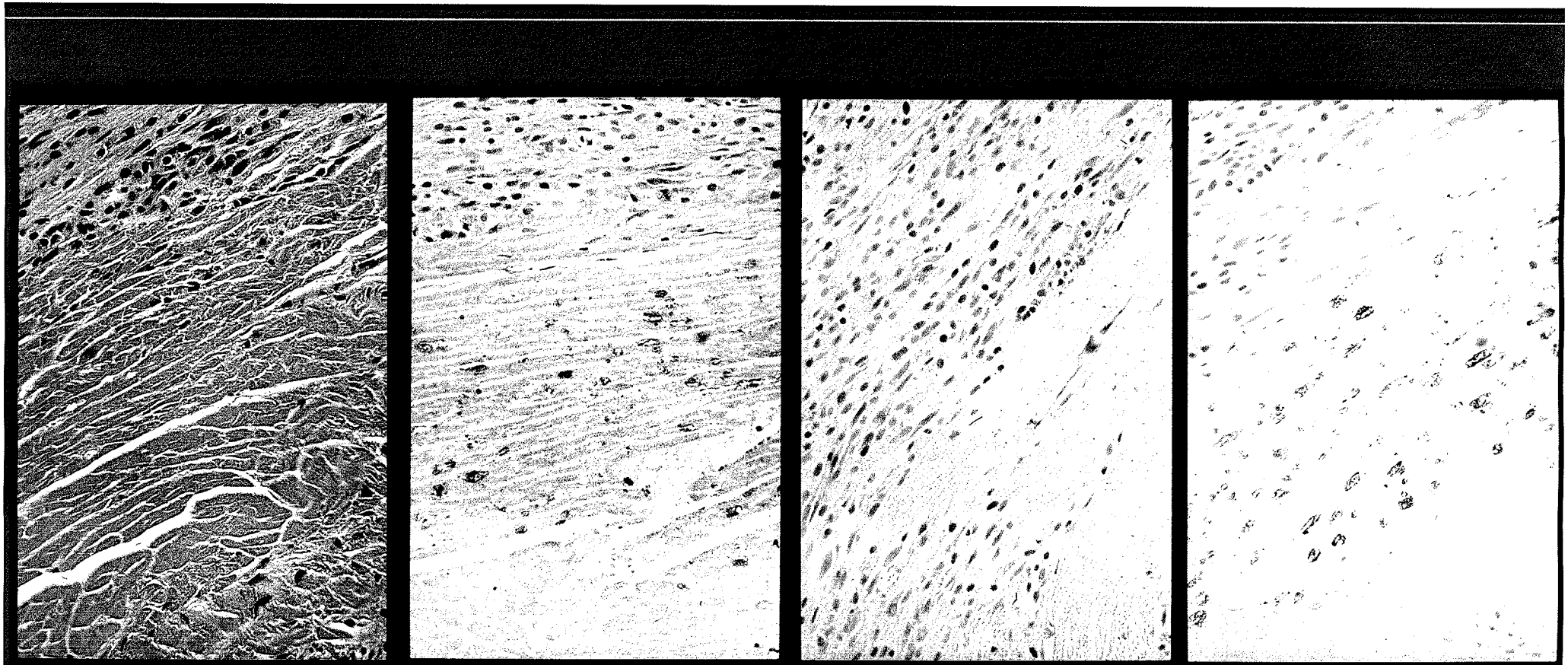
Complement dependence of enhancement of MI size by human CRP

Treatment	Day 5 survivors	Infarct size % mean (SD)	Bonferroni t-test
Buffer	8/ 8	14.3 (1.2)	
Human CRP	3/ 5	19.7 (1.6)	P=0.0020
C depletion	5/ 5	6.5 (0.9)	P=0.0000
C depletion + human CRP	6/ 6	6.9 (0.3)	P=0.0000

Infarcts 38% larger in rats receiving human CRP

Infarcts ~50% smaller in complement depleted rats

Deposition of human CRP and rat C3 in rat myocardial infarction



H & E | Anti-CRP | Absorbed anti-CRP | Anti-C3

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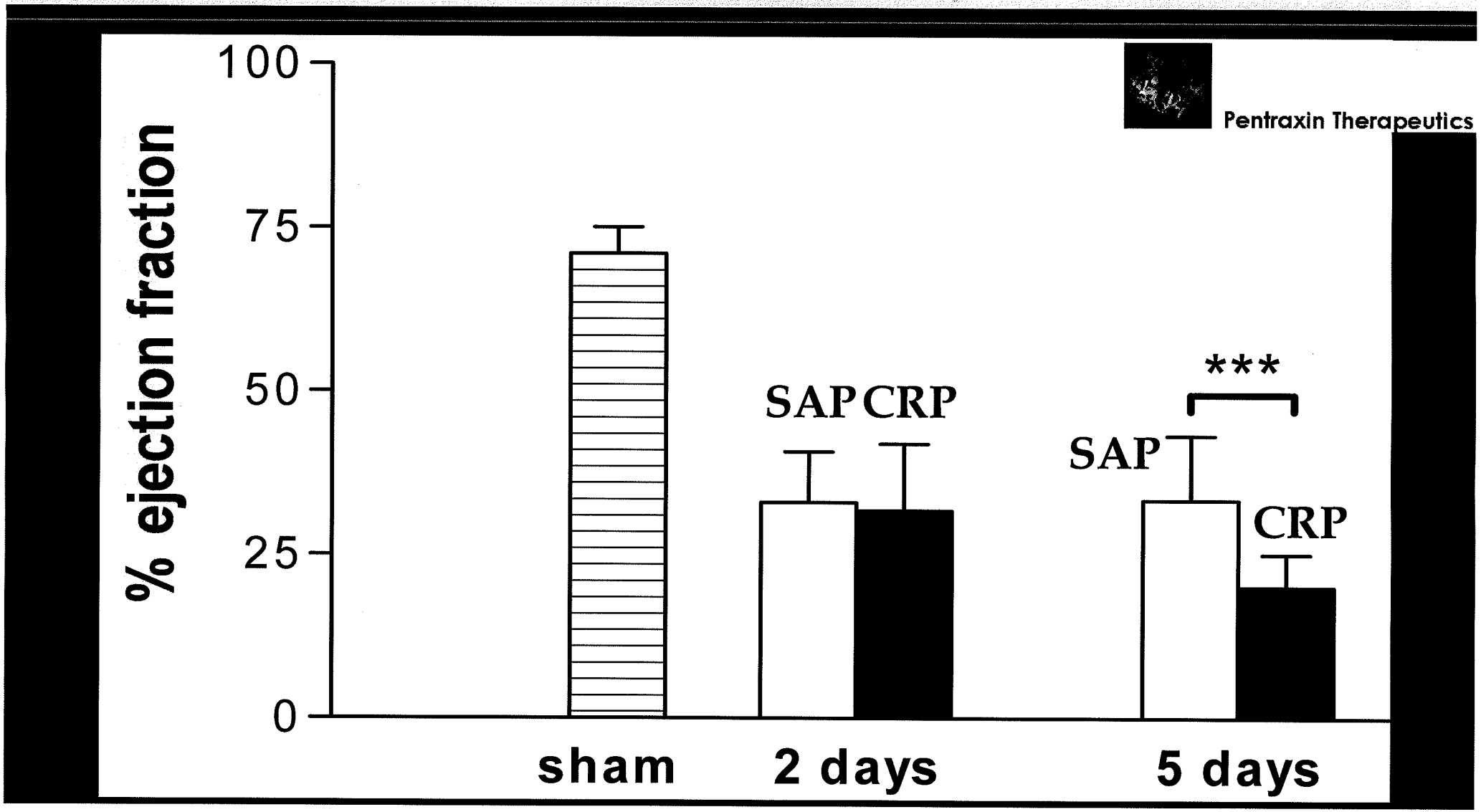
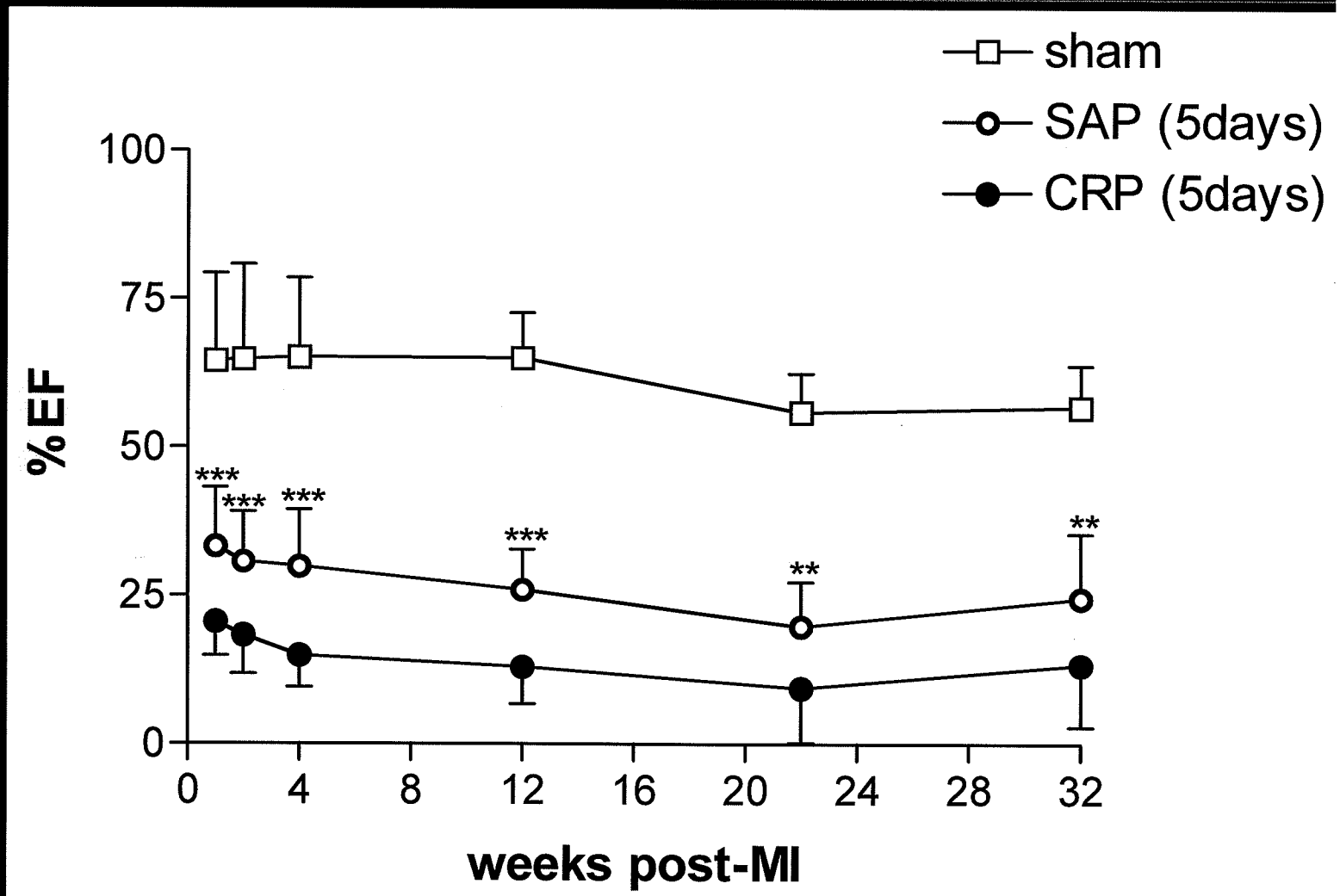
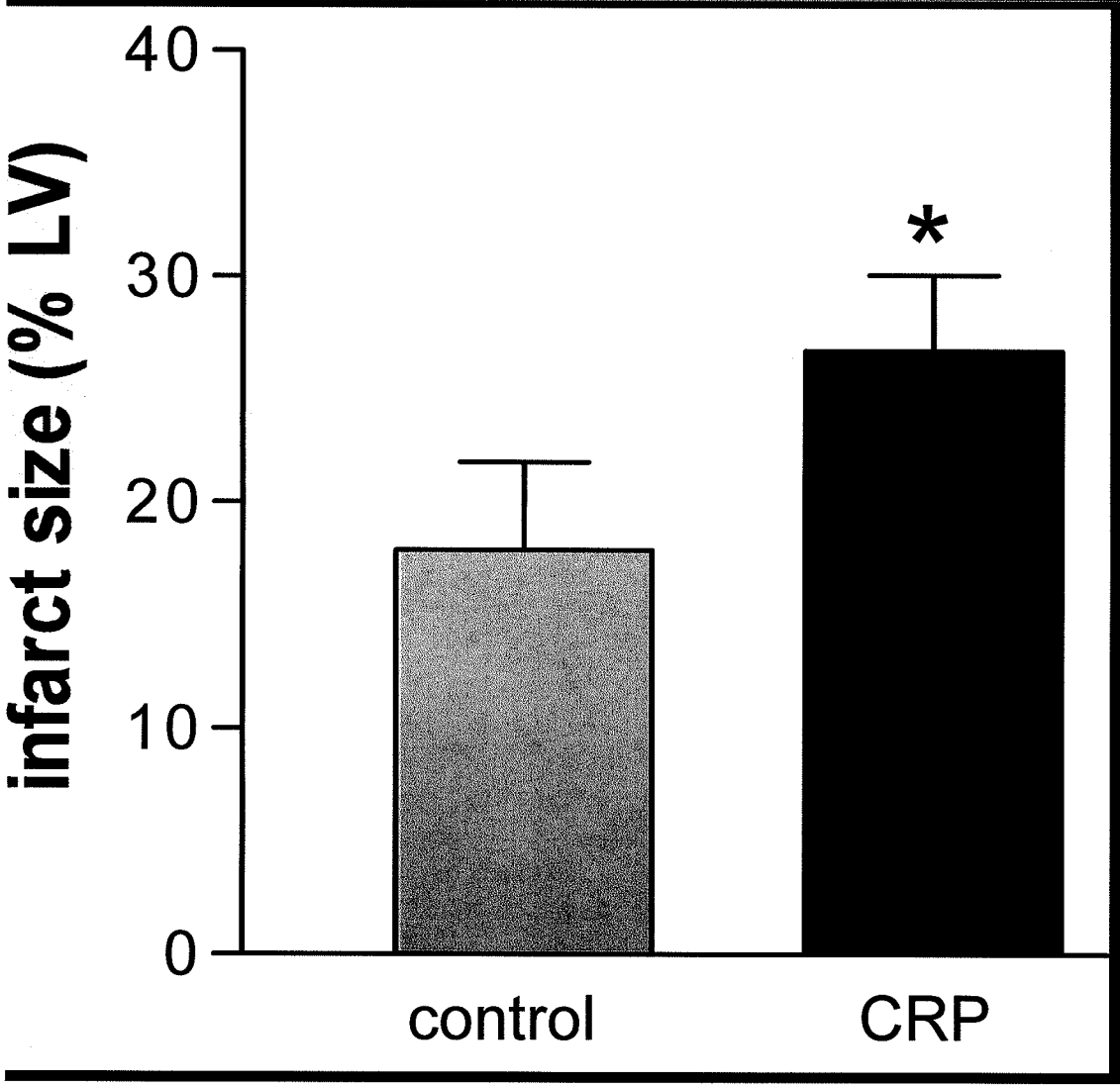
EF one week after coronary artery ligation



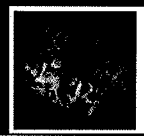
EF after coronary artery ligation & injection of human CRP or SAP



Myocardial infarction size at 32 weeks



5 daily doses of 40 mg/kg human CRP or SAP after coronary artery ligation



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Effect of human CRP on myocardial IR injury in rats

40 min ischemia

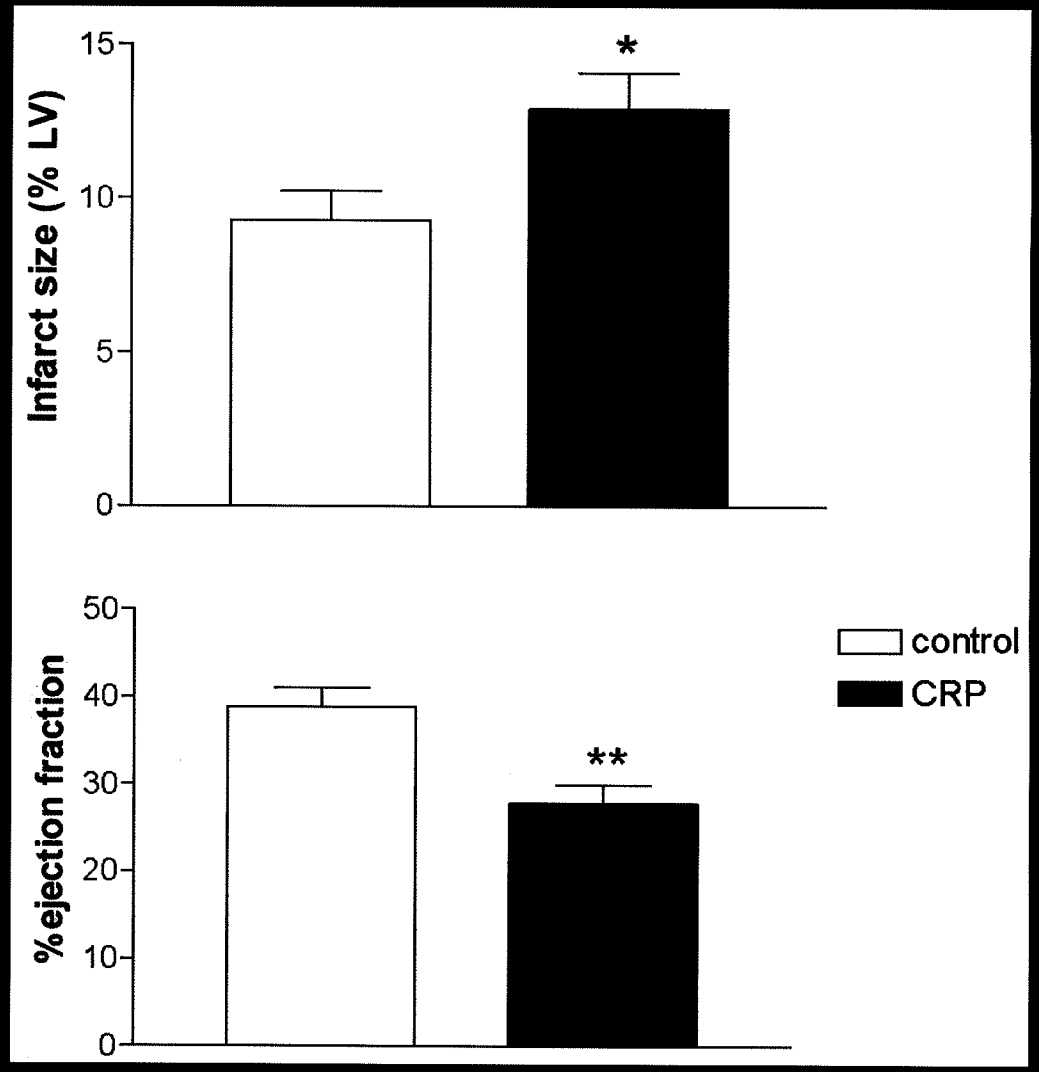
Assess at day 5

Controls n=9

CRP n=10

Infarct size: P=0.0283

EF: P=0.00179



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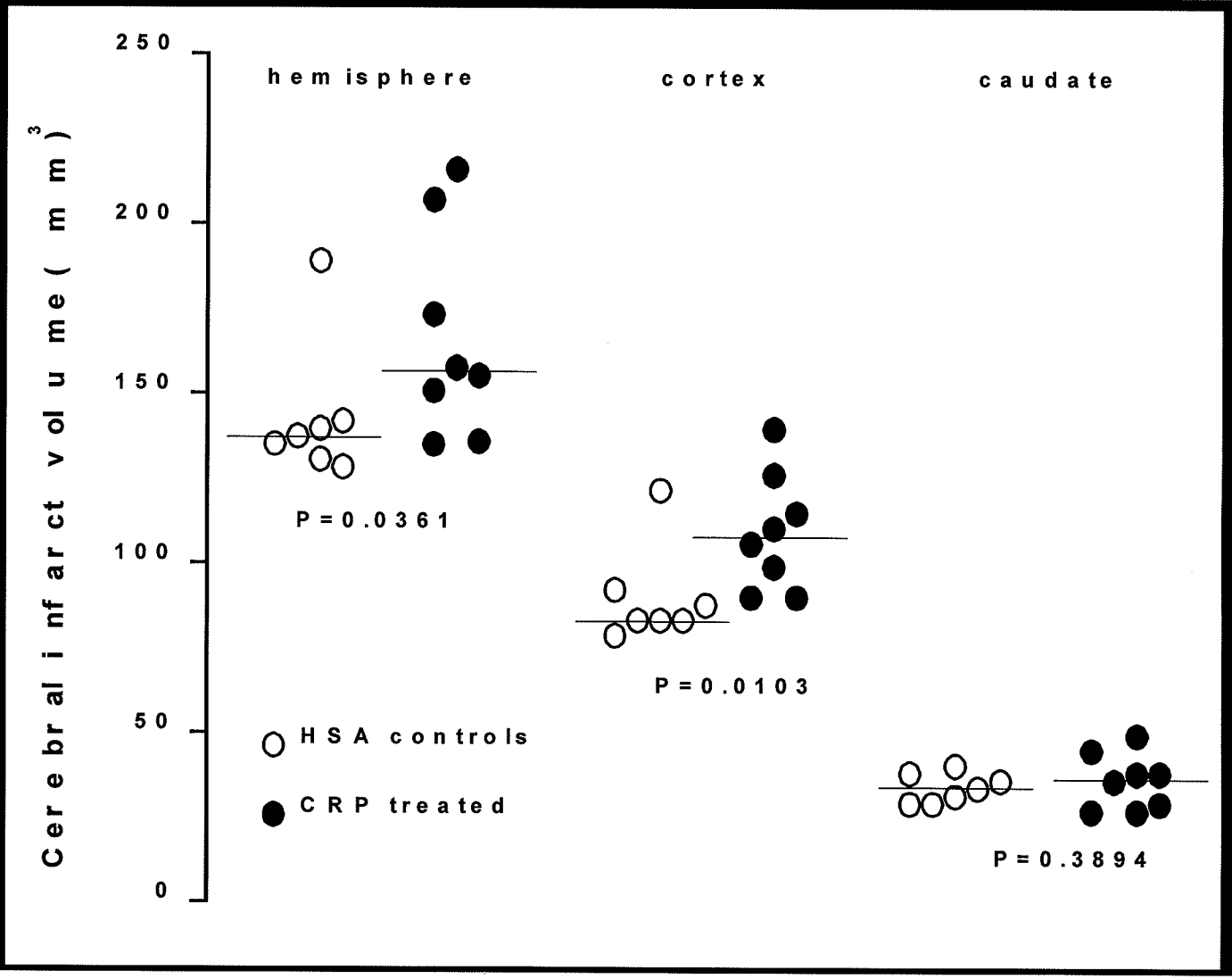
Human CRP increases cerebral infarct size in rats



PROOF THAT HUMAN CRP INCREASES TISSUE DAMAGE *IN VIVO*

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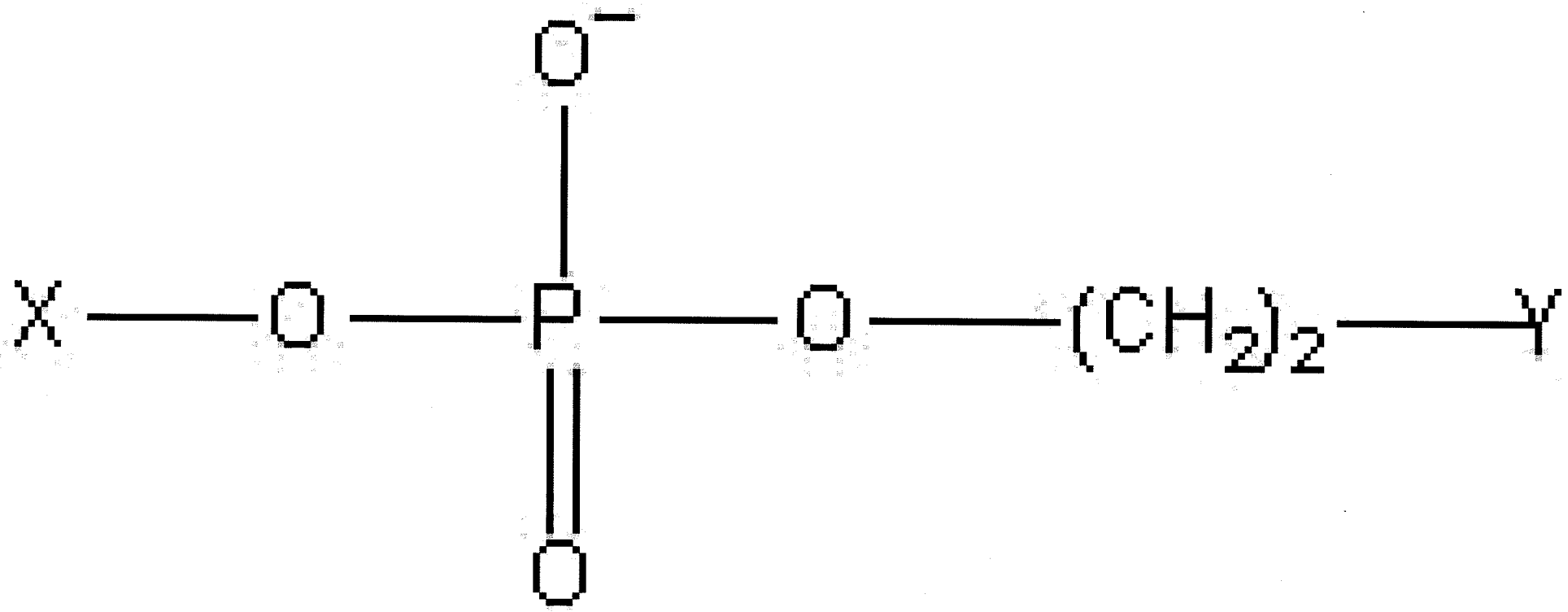
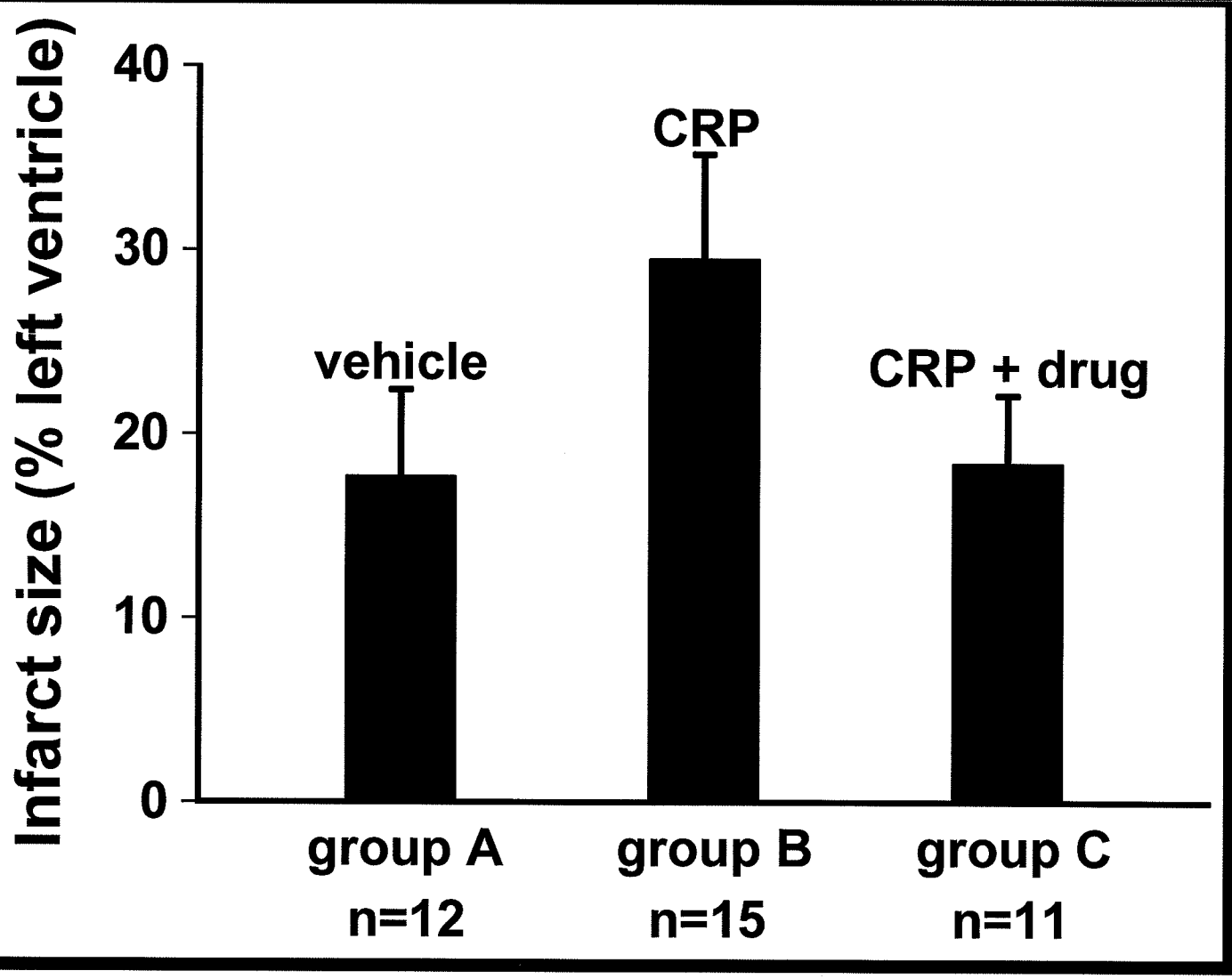
Formula of phosphocholine derivative drugs

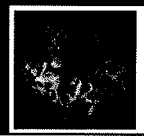


Phosphocholine derivative inhibits pathogenic effect of human CRP *in vivo*



Survivors at d5:
A 12/13
B 15/21
C 11/11

Drug alone:
no effect despite
complete inhibitio
of rat CRP



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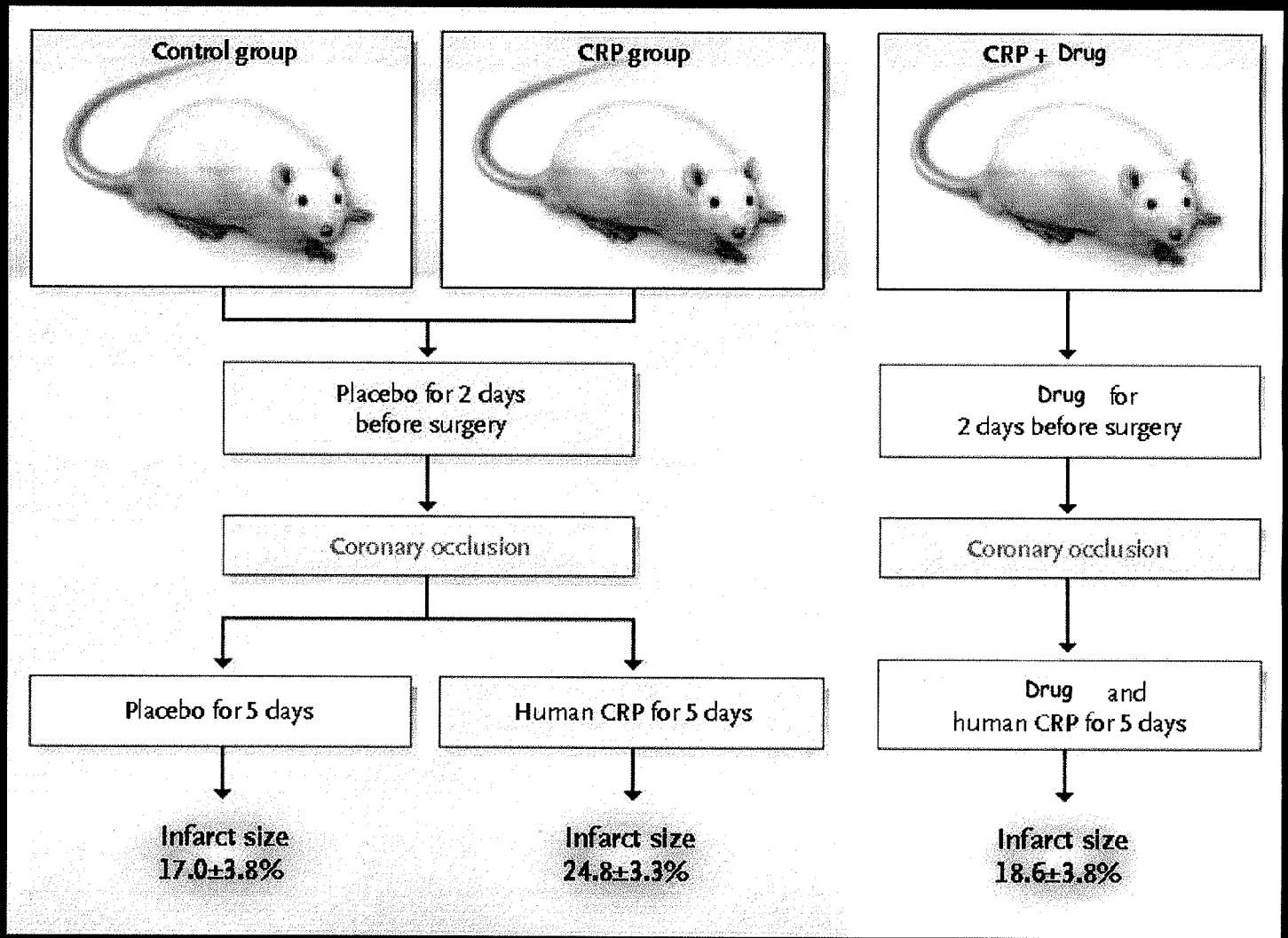
Phosphocholine derivative inhibits pathogenic effect of human CRP *in vivo*

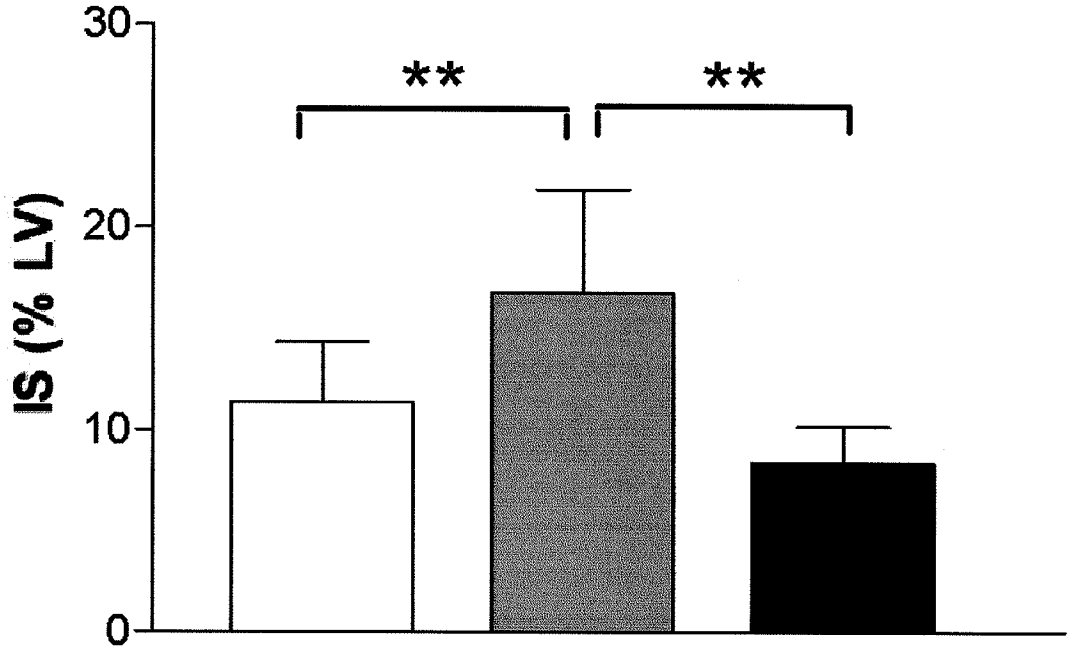
Kitsis & Jialal, 2006, *New England Journal of Medicine*, 355: 513-5

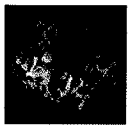


Phosphocholine derivative inhibits effect of human CRP in IR injury

One-way ANOVA
Bonferroni's post-test, mean ±SD
(**p<0.01)

cont (n=10)
CRP (n=12)
drug + CRP (n=9)





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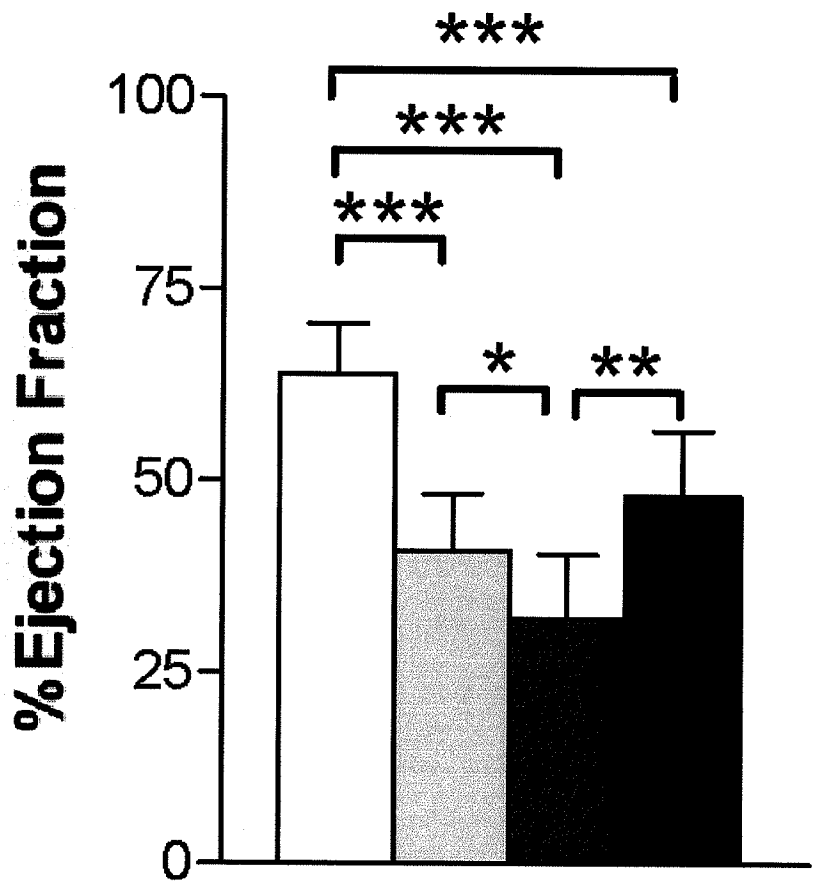
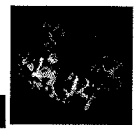
Phosphocholine derivative inhibits effect of human CRP in IR injury

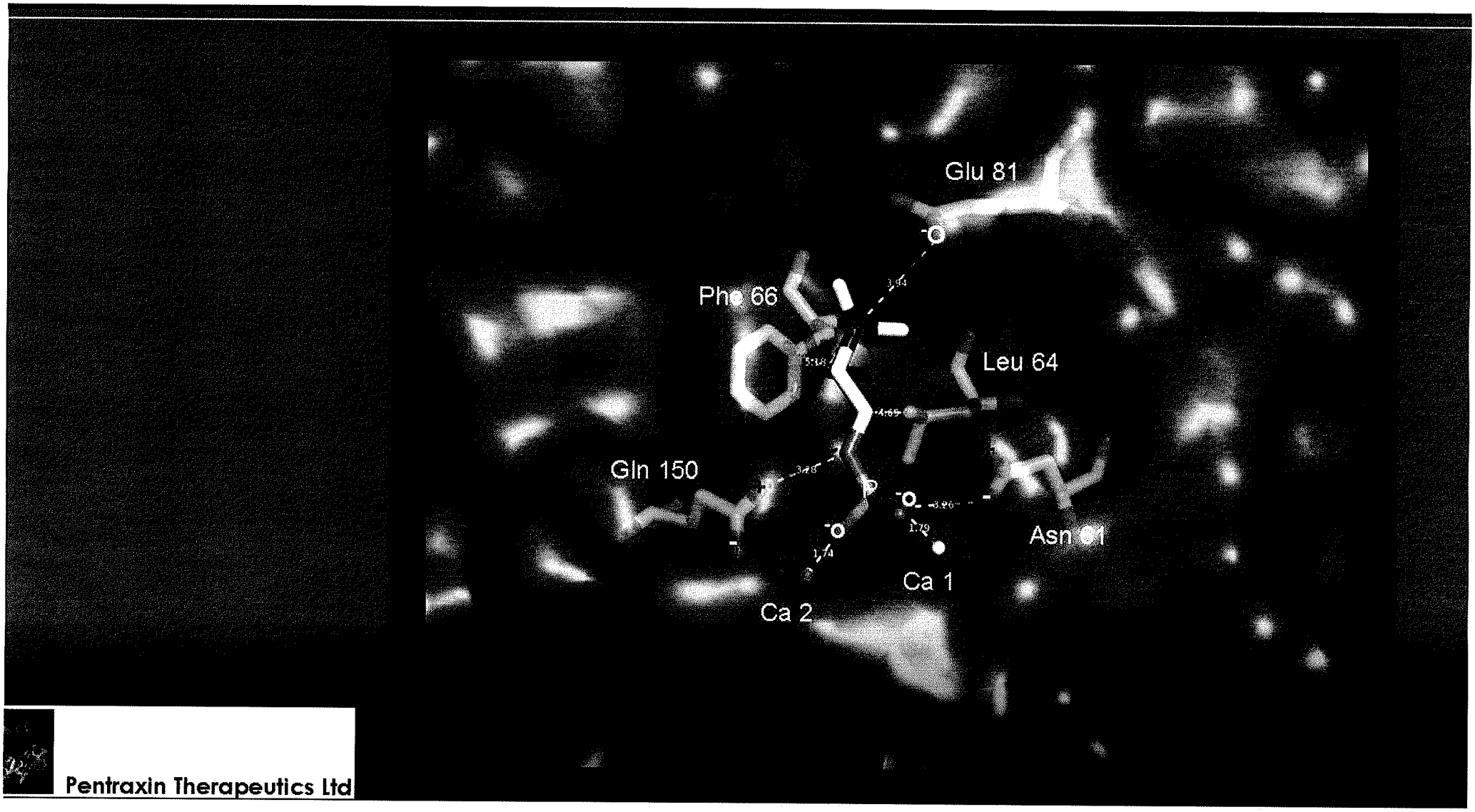


Mean ±SD, One-way ANOVA
(Bonferroni's post-test
*p<0.05, **p<0.01, ***p<0.001)

- cont sham
- cont CAL
- CRP
- CRP+drug



Binding of phosphocholine by CRP



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Other CRP ligands

- Agar, barium sulfate: Ganrot PO, Kindmark CO. A simple two-step procedure for isolation of C-reactive protein. Biochim Biophys Acta. 1969 ;194:443-8.
- Phosphorylated cellulose: Riley RF, Coleman MK. Isolation of C-reactive proteins of man, monkey, rabbit and dog by affinity chromatography on. Clin Chim Acta. 1970 30:483-96.
- Sulfated polyacrylamide: Pepys MB, Dash AC, Ashley MJ. Isolation of C-reactive protein by affinity chromatography. Clin Exp Immunol. 1977 30:32-7.

CONCLUSIONS

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Reduction of tissue damage

- In the presence of ischemic necrosis in the heart, CRP causes increased muscle damage
- In the presence of stroke, CRP causes increased brain damage
- Inhibition of CRP binding *in vivo* abolishes this extra damage
- Phosphocholine drugs are effective CRP inhibitors
- Claimed invention is an enabled pioneer invention, not taught or suggested by prior art